UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,910	09/09/2003	Kenichi Chiba	2003946-0056 (ANDI/CIP)	5169

24280 7590 03/16/2006

CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
BALLS, ROBERT J	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/657,910	CHIBA ET AL.	
	Examiner	Art Unit	
	James Balls	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,27-31,33,36,38-40,42,43 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,27-31,33,36,38-40,42,43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-24, 27-31, 33, 36, 38-40, 42-43 and 45 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-20, 36, 38-40, 42 and 45 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dombrowski et al., *Production of a Family of Kinase-Inhibiting Lactones from Fungal Fermentations*, THE J. ANTIBIOT., 52:12 1077-85 (1999) in view of Patani and LaVoi, *Bioisosterism: A Rational Approach in Drug Design*, CHEM. REV. 96:3147-76 (1996). The instant claims are drawn to a zearalenone-like marcrolide wherein R_9 can be a variety of different functional groups including hydrogen, halogen, thiol and amine. Dombrowski et al. disclose a zearalenone-like macrolide wherein R_9 is a hydroxyl or methoxy but not a hydrogen, halogen, thiol, amine, etc. Patani & LaVoi show that NH_2, Cl, and CN are bioisosteres of methoxy (P. 3154, Table 14) and that Cl, CH_3, H, and NH_2 are bioisosteres of phenolic hydroxyl (P. 3153, Table 12). Motivation to combine these references is found in Patani &LaVoie where they explain the concept of bioisosterism is considered intuitive and is a common approach used by medicinal chemists in the development of drugs. Patani & LaVoie, P. 3147, Introduction. Based

on these references, it would have been obvious to a person of ordinary skill in the art to replace R_9 with a bioisostere of hydroxyl or methoxy and preserve activity, rendering the instant claims unpatentable.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claim Rejections - 35 USC § 112, first paragraph

4. Claims 1-24, 27-31, 33, 36, 38-40, 42-43 and 45 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amended claims provide a new grouping of R_9 constituents that is not supported by the originally filed application. The original group of constituents included "hydroxyl, protected hydroxyl and OR_{12}", which were removed in the amended claims to overcome prior art. The original disclosure does not support this new grouping of R_9

constituents. However, the specification has an individual embodiment that supports a claim wherein R_9 is $NH_{12}R_{13}$. (Specification page 17, Paragraph [0075]). The specification also has an individual embodiment that supports a claim wherein R_9 is – $X(CH_2)_pX_2$-R_{14}. (Specification p. 18, Paragraph [0079]). Because the specification does not support the amended claim's current grouping of R_9-constituents, it constitutes new matter and renders the instant claims unpatentable under 35 U.S.C. §112.

5. Claims 1-24, 27-31, 33, 36, 38-40, 42-43 and 45 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for R_9 being hydroxy, does not reasonably provide enablement for R_9 being other constituents. A person skilled in the art is not enabled to use the invention commensurate in scope with the instant claims. The specification provides many examples and methods of making zearalenone-like marcrolides wherein R_9 is a number of substituents other than hydroxy. However, data showing that these compounds actually exhibit biological activity does not exist. Conversely, the prior art suggests that deviating from an R_9-hydroxy group will eliminate biological activity. Johnston et al., *Synthesis of Dideoxyzearalanone and Hydroxyl Derivatives*, J. MED. CHEM., 13(5):941-44 (1970). The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without

undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Courts rely on the following factors set out in *In re Wands* to determine whether undue experimentation is required to practice a claimed invention, i.e. whether the claimed invention is enabled: (a) The breadth of the claims; (b) The nature of the invention and predictability in the art; (c) The state of the prior art; (d) The level of one of ordinary skill; (e) The amount of direction provided by the inventor; (f) The existence of working examples; and (g) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Id.* The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407.

The analysis is applied to the instant case.

(a) The claims are broad due to the high number of compounds they embody. For instance, the compound of Claim 1 encompasses an enormous variety of compounds due to the number and breadth of its variables (i.e. Y, Z, R_1-R_{10}).

(b) The invention is physiological in nature as it is directed toward pharmaceuticals and treating diseases with those pharmaceuticals, an art which is highly unpredictable. "[T]he scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In the highly unpredictable pharmaceutical art, the required disclosure is greater than for the disclosure of an invention involving predictable factors

such as mechanical or electrical elements. *In re Vaeck*, 20 USPQ 2d 1438 (CAFC 1991).

(c) The prior art suggests that deviating from a R_9-hydroxy group has dramatic effects on the biological activity of zearalenone derivatives. Johnston et al., *Synthesis of Dideoxyzearalanone and Hydroxyl Derivatives*, J. MED. CHEM., 13(5):941-44 (1970). Johnston et al. synthesized and tested dideoxyzearalone and its hydroxyl derivates for estrogenic activity and found that changing the hydroxyl group at the 4'-position (applicants' R_9-position) resulted in less than 0.1 the activity of zearalenone. Johnston et al., p. 942, Biological Evaluation.

(d) The level of skill required to practice the invention is high due to its pharmaceutical nature.

(e) The specification shows how to make the claimed compounds but fails to demonstrate that they maintain biological activity. The specification includes statements alleging that the compounds discloses therein exhibit NF-kB inhibitory activity but does not provide any data in support thereof. Specification p. 24, Paragraphs [0229]-[0230] and page 292 Paragraphs [1438]-[1449].

(f) The specification contains no working examples demonstrating the biological activity of the claimed compounds.

(g) The quantity of experimentation necessary to make or use the disclosed invention is high based on the breadth of the claims, the contradictory art, the limited guidance in the specification, and the high degree of skill required to practice the invention. A person of ordinary skill in the art would be subjected to undue

experimentation in order to make and use the invention, and therefore, the invention is not enabled.

Conclusion

6. No Claims are allowed.

7. Claims 1-20, 36, 38-40, 42 and 45 are rejected under 35 U.S.C. §103.

8. Claims 1-20, 36, 38-40, 42 and 45 are rejected under 35 U.S.C. §112, written description.

9. Claims 1-24, 27-31, 33, 36, 38-40, 42-43 and 45 are rejected under 35 U.S.C. §112, enablement.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Balls whose telephone number is (571) 272-7997. The examiner can normally be reached on Mon - Fri 8:00am - 4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James Balls
Examiner
Art Unit 1625

Cecelia Tsang
Supervisory Patent Examiner
Art Unit 1625